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Received: 23 September 2021 | Accepted: 30 December 2021

DOI: 10.1111/liv.15157

Liver INTERNATIONAL WILEY

REVIEW

Integrins as a drug target in liver fibrosis

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Funding information
GPA, JIG and SRR are supported by National Institute of Health Research Nottingham Biomedical Research Centre. SRR is part funded by GlaxoSmithKline. JAR is a former employee of GlaxoSmithKline and current employee at Galecto Biotech. KTP is a current employee of GlaxoSmithKline.

Handling Editor: Luca Valenti

Abstract

As the worldwide prevalence of chronic liver diseases is high and continuing to increase, there is an urgent need for treatment to prevent cirrhosis-related morbidity and mortality. Integrins are heterodimeric cell-surface proteins that are promising targets for therapeutic intervention. αv integrins are central in the development of fibrosis as they activate latent TGFβ, a known profibrogenic cytokine. The αv subunit can form heterodimers with β1, β3, β5, β6 or β8 subunits and one or more of these integrins are central to the development of liver fibrosis, however, their relative importance is not understood. This review summarises the current knowledge of αv integrins and their respective β subunits in different organs, with a focus on liver fibrosis and the emerging preclinical and clinical data with regards to αv integrin inhibitors.

KEYWORDS
fibrosis, integrins, liver cirrhosis, liver disease, non-alcoholic steatohepatitis

1 | INTRODUCTION

1.1 | Liver fibrosis

Liver fibrosis occurs in most chronic liver diseases (CLD),[1] affecting an estimated 844 million people worldwide and having a mortality rate of two million deaths per year.[2] It is the excessive deposition of extracellular matrix (ECM) proteins and results from persistent and chronic injury to the liver which may be caused by hepatitis C infections, alcohol excess and non-alcoholic steatohepatitis (NASH).[1]

The majority of CLDs follow a pattern where recurrent or persistent injury is associated with inflammation, followed by fibrosis

Abbreviations: ACC, Acetyl-CoA carboxylase; ALK, Activin receptor-like kinase; ASK1, Apoptosis signal-regulating kinase 1; BDL, Bile duct ligation; C8, Compound 8; CCL, Chemokine ligand; CCL_4, Carbon tetrachloride; CCR, Chemokine receptor type; CLD, Chronic liver disease; DAMP, Damage-associated molecular patterns; DGAT2, Diacylglycerol O-acyltransferase 2; ECM, Extracellular matrix; ERK, Extracellular-signal-regulated kinase; FGF, Fibroblast growth factor; FGFR, Fibroblast growth factor receptor; FXR, Farnesoid X receptor; HMGB1, High-mobility group box protein 1; HSC, Hepatic stellate cells; IC_{50}, Inhibitory concentration; IL, Interleukin; IPF, Idiopathic pulmonary fibrosis; K_D, Dissociation constant; KLB, β-klotho; MAPK, Mitogen-activated protein kinase; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; PDGF, Platelet derived growth factor; PET, Positron emission tomography; PI3, Phosphoinositide 3; RGD, Arginine, glycine and aspartate; ROS, Reactive oxygen species; TGFα, Transforming growth factor α; TGFβ, Transforming growth factor β; THR-β, Thyroid hormone receptor β; TLR4, Toll-like receptor 4; TNFα, Tumour necrosis factor α; UUO, Unilateral ureteral obstruction.

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and finally cirrhosis, leading to altered hepatic function.[3] The presence and severity of fibrosis predict both cirrhosis development and long-term survival.[4]

Although fibrosis initially starts by being part of the tissue repair process, it becomes pathogenic when it is not controlled.[5] In tissue fibrogenesis, integrins, which are heterodimeric cell surface transmembrane receptors, mediate various cell-matrix and cell-cell interactions.[6,7] In idiopathic pulmonary fibrosis (IPF), αvβ6 integrin has been shown to be a potential biomarker of fibrosis[6] as expression increases in the lung following injury[8] and is correlated with poor prognostic outcome.[9] Furthermore, in both rodent models of liver fibrosis and patients with CLD, αvβ6 integrin expression has been shown to be markedly upregulated.[10] Alternative studies have suggested that the major integrin driving tissue fibrosis in the liver and lung is αvβ1 integrin. This is supported by data showing that administration of the αvβ1-specific small-molecule integrin inhibitor compound 8 (c8), resulting in the partial reversal of liver and lung fibrosis in rodent models.[11]

Initially, fibrosis was thought to be irreversible, with tissue scarring being deemed permanent. However, there is now compelling evidence for the resolution of fibrosis in the liver.[12] Patients with liver fibrosis due to viral hepatitis showed regression of fibrosis after treatment with antiviral therapies, suggesting that liver fibrosis can be reversed through addressing the underlying cause of the fibrosis.[13] The liver also has an extraordinary capacity to regenerate in comparison to organs such as the lungs and kidneys. This may make the liver a more attractive target to reverse fibrosis compared to other organs.

Key points

- There are not any approved treatments for liver fibrosis with the current drug pipeline targeting anti-inflammatory pathways and/or lipid metabolism/steatosis rather than fibrosis.
- αv integrins which form heterodimers with β1, β3, β5, β6 or β8 subunits are central to the development of liver fibrosis and have the potential to be a promising anti-fibrotic target, however, their specific role is not completely understood.
- Preclinical models, as well as preclinical and clinical data using αv integrin inhibitors have shown certain αv integrins to be a potential target in various fibrotic diseases including liver fibrosis.

2 | ROLE OF INTEGRINS IN LIVER FIBROSIS

2.1 | Cellular mechanisms of liver fibrosis

The progression of fibrosis is complex and involves parenchymal, non-parenchymal, as well as infiltrating immune cells. During liver injury, hepatocyte death via apoptosis, necrosis or necroptosis triggers activation of inflammatory and fibrogenic pathways. This occurs in cells such as hepatic stellate cells (HSCs), hepatocytes and Kupffer cells which all interact and promote the secretion of pro-inflammatory and/or profibrogenic cytokines[1,14–16] (Figure 1). HSCs are the primary effector cells in liver fibrosis[17] and are considered to be the main source of hepatic myofibroblasts, the major hepatic ECM-producing cells.[15] In response to chronic liver injury, quiescent HSCs are activated and change their morphology transdifferentiating to myofibroblasts.[1]

Transforming growth factor β (TGFβ) is a key regulator of liver physiology and pathology. It contributes to all stages of disease progression, from initial liver injury, to fibrosis and then cirrhosis. It is known as a profibrogenic cytokine due to its role in HSC activation and ECM production.[18] HSCs become activated as a result of reactive oxygen intermediates, apoptotic bodies and paracrine stimuli from neighbouring cell types in response to liver injury[19] and as a result HSCs secrete latent TGFβ. The activation of latent TGFβ by integrins is a major mechanism[20] that leads to an autocrine positive feedback loop being formed which drives fibrogenesis.[21]

2.1.1 | An overview of integrins and their role in health and disease

Integrins are present in all nucleated cells and multiple subtypes can be expressed simultaneously. There are 24 known integrin heterodimers that arise from noncovalent associations between 18 different α-subunits and 8 β-subunits.[22,23] Integrins can be broadly grouped into families according to these ligand binding or expression specificities. For example, Arg-Gly-Asp (RGD) integrins recognise proteins containing the RGD peptide motifs (notably present on latent TGFβ), collagen receptors, laminin receptors and leukocyte-specific integrins.[24,25] The regulatory effect of integrins on TGFβ activity appears to primarily involve αv-containing integrins that selectively bind to the RGD motif on latent TGFβ, activating TGFβ.[20,26] Of the 8 members in this family of RGD integrins, 5 contain the αv subunit, with αvβ6 and αvβ8 integrins having the highest affinity for latent TGFβ.[20,25,26] In activated HSCs, αvβ1, αvβ3, αvβ5 and αvβ8 integrins have been shown to be expressed[27] with αvβ3 and αvβ5 integrins expressed on endothelial cells. These cells promote the activation of HSCs.[28] Additionally, αvβ6 integrin has also been shown to be expressed on activated cholangiocytes[29] which are important drivers of fibrogenesis in biliary liver diseases and in more advanced stages of liver fibrosis of all etiologies.[28]

Integrins are involved in a wide range of cellular processes and are the main cell adhesion receptors for the components of the ECM. They are activated by a variety of extracellular ligands which include ECM ligands, causing them to undergo conformational changes[22,24,26] which are more complex than other cell surface receptors.[23,30] Integrins sense both chemical and physical properties of the ECM,

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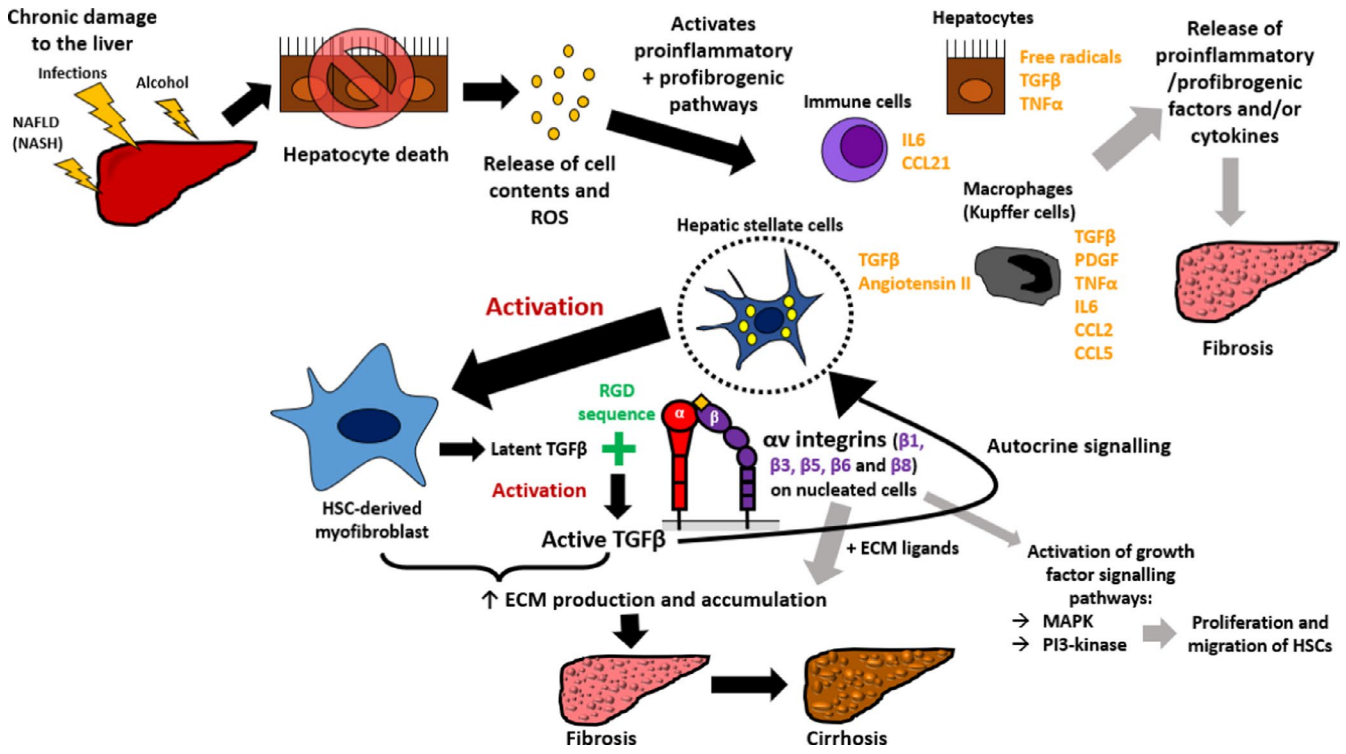

FIGURE 1 Overview of the cellular mechanism of fibrosis in the Liver. Chronic damage as a result of infection, alcohol abuse and/or NAFLD leads to hepatocyte death which releases cellular contents (eg DNA and potentially DAMPs such as ATP, formyl peptides and HMGB1) and ROS. This induces the activation of proinflammatory and profibrogenic pathways in various cells present in the liver. These cells are involved in driving fibrosis by releasing proinflammatory/profibrogenic factors and/or cytokines/chemokines (highlighted in orange) and these can drive the activation of HSCs into myofibroblasts. IL6 and TNFα are both proinflammatory cytokines. TNFα induces hepatocyte apoptosis, neutrophil activation and promotes HSC survival and proliferation. The chemokine CCL21 results in the induction of proinflammatory genes in HSCs and CCL2 and CCL5 stimulate the influx of immune cells. Furthermore, CCL5 recruits and activates HSCs. Resident macrophages known as Kupffer cells are notably known to promote the survival of activated HSCs through releasing TGFβ and PDGF. They are the main producers of PDGF which is a predominant mitogen for activated HSCs. HSCs are considered to be the major source of myofibroblasts which contribute to 90% of the ECM. HSCs release angiotensin II which stimulates cell proliferation, migration, collagen synthesis and secretion of proinflammatory cytokines. More importantly, activated HSCs secrete latent TGFβ and form an autocrine positive feedback loop. The latent TGFβ contains an RGD sequence which has a high affinity for integrin molecules and once this interaction occurs, active TGFβ is released. TGFβ has a role in HSC activation and ECM production. Integrins αvβ1, αvβ3, αvβ5, αvβ6 and αvβ8 in the extended open conformation state have the highest affinity for TGFβ and once they are activated it leads to stimulation of growth factor signalling pathways such as MAPK and PI3-kinase pathways that regulate cell proliferation, survival and/or growth. These pathways mediate proliferation and migration of HSCs and are necessary for PDGF-induced proliferation. The release of proinflammatory factors, growth factors, and cytokines from various cells, in addition to the activities of myofibroblasts, binding of integrins both to the ECM and TGFβ, results in ECM accumulation and fibrosis which then ultimately leads to cirrhosis. CCL, chemokine ligand; DAMP, damage-associated molecular patterns; ECM, extracellular matrix; HMGB1, high-mobility group box protein 1; HSC, hepatic stellate cell; IL, interleukin; MAPK, mitogen-activated protein kinase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PDGF, platelet derived growth factor; PI3-kinase, phosphoinositide 3-kinase; RGD, arginine, glycine and aspartate; ROS, reactive oxygen species; TGFβ, transforming growth factor β; TNFα, tumour necrosis factor α

binding extracellularly to the ECM and intracellularly to the cytoskeleton, thereby linking the extracellular environment with the cell interior.[22] Cooperation with growth factors, ECM components and co-receptors results in integrins being able to generate an integrated signal, fine-tuned to the precise external environment.[31,32] Integrin activation and binding to the ECM triggers complex and highly dynamic machinery responsible for regulating aspects of cell fate such as survival, migration, polarity and differentiation.[22,26]

Interactions of integrins with ECM ligands specifically results in the remodelling of the ECM.[22,26] The pathways that are activated depend on the nature of the binding and include integrin-linked kinase and growth factor signalling pathways such as the mitogen activated protein kinase (MAPK) and phosphoinositol 3-kinase pathways,[31] pathways regulating cell proliferation, survival and growth.[33,34] Hence, the dysregulation of integrin-mediated adhesion, signalling and in particular, the activation of latent TGFβ, is a precursor in the pathogenesis of diseases such as fibrosis[22,24,35] (Figure 1).

Integrin antagonists have attracted attention as potential therapeutic targets for fibrosis as they are already well-established therapeutics for cardiovascular diseases.[36] For example, αIIbβ3 integrin antagonists, abciximab, eptifibatide and tirofiban are used to inhibit thrombosis.[37] Small-molecule integrin antagonists fall

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into three different classes that each relate to a specific integrin conformation state (Figure 2). The antagonists can either interfere with ligand binding or stabilise a particular integrin conformation. Most antagonists stabilise the extended, high-affinity integrin conformation.[36] There have been efforts to develop antagonists that effectively inhibit high affinity conformations, however, none have been translated to successful therapies. Suggestions are that they have either insufficient specificity or systemic toxicity but details have not been disclosed.[38] In addition to this, the functional consequences of the antagonist-induced active conformation has been debated with agonistic effects not clear. For example, αIIbβ3 inhibitors stabilise the high-affinity integrin conformation and failed phase 3 trials which could be due to the unintended partial agonist effects. Further structural work on integrins and their complexes in order to understand the conformation change during activation should accelerate the development of current and novel classes of integrin antagonists, especially for allosteric inhibitors.[36,38]

2.2 | TGFβ and αv integrins

A large body of evidence points to the importance of TGFβ and αv integrins in tissue fibrosis. TGFβ signalling has been shown to upregulate expression of specific integrins.[39] For example, treatment of human WI-38 lung fibroblasts cell line with TGFβ led to increased αvβ3 and β1 integrin expression by ~3- and 2-fold respectively.[40,41] Similarly, in human keratinocytes, TGFβ increased the expression of αvβ5 integrin ~4-fold and it induced αvβ6 integrin expression, thereby further driving TGFβ activation effects.[42]

In models of pulmonary and renal fibrosis, αvβ6 integrin has been shown to be the main class involved in latent TGFβ activation during fibrosis development. For example, the reduced fibrotic response from bleomycin and ureteral obstruction-induced fibrosis in β6 integrin knockout mice was suggested to be due to the lack of active TGFβ as shown through the little staining detected using immunohistochemistry.[43,44] Both αvβ3 and αvβ5 integrins are suggested to activate TGFβ in scleroderma fibroblasts to promote the transformation of these cells into myofibroblasts. Assessment of TGFβ activation in a co-culture model comprising murine HSCs and a TGFβ reporter (plasminogen activator inhibitor 1-luciferase) cell line demonstrated TGFβ activation was inhibited by an αvβ1 integrin inhibitor, c8. Similar results were also observed using human IPF lung fibroblasts and in murine renal fibroblasts. Inhibitory concentrations (IC_{50}) of c8 in this co-culture system ranged from 0.35nM to 0.5nM for HSCs and lung fibroblasts, as well as 1nM for renal fibroblasts. These data suggest that αvβ1 integrin is an important integrin expressed by liver HSCs, lung and kidney fibroblasts, which is at least in part responsible for activation of latent

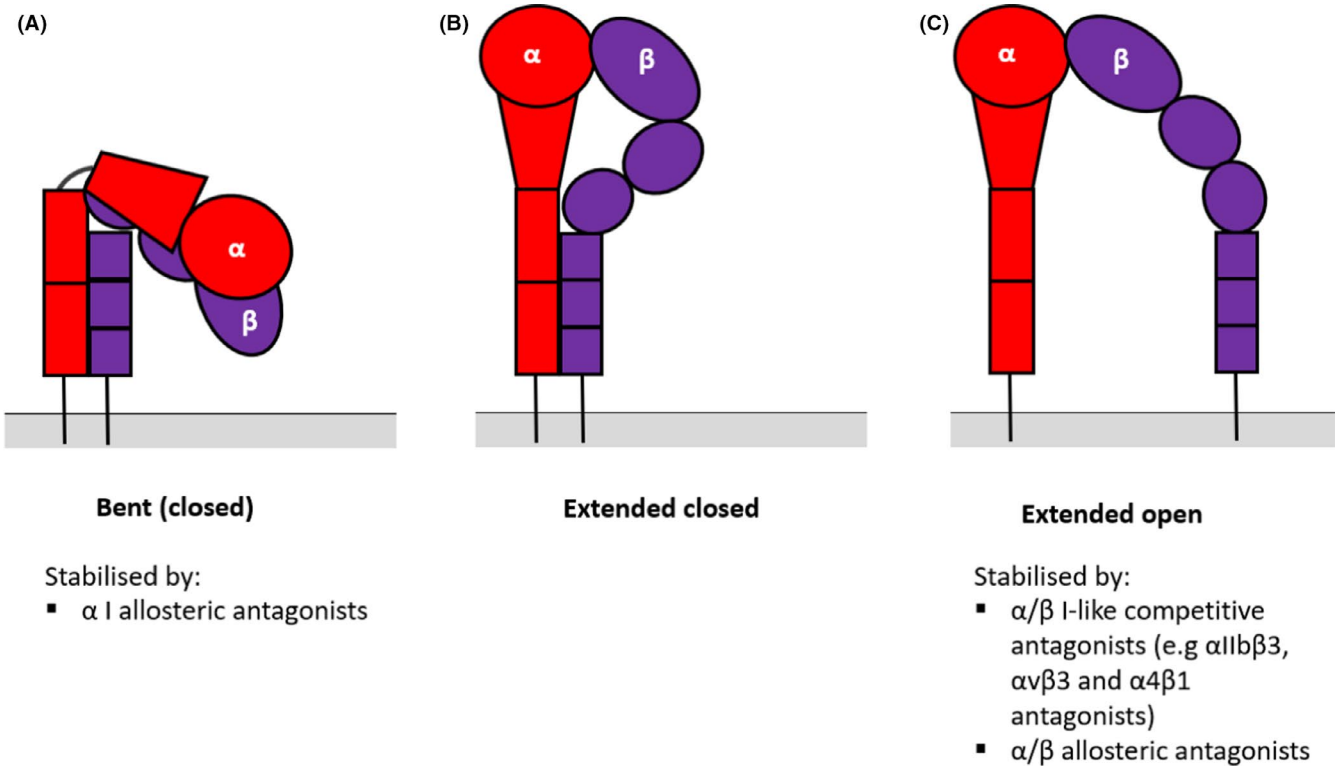

FIGURE 2 The conformational states of integrins. Overall, there are three integrin conformational states. These are known as the (A) bent (closed), (B) extended closed and (C) extended open conformations. In a resting, bent-closed conformation, the ligand-binding site lies close to the plasma membrane and has a low ligand affinity. In the two extended states, the ligand-binding site faces away and extends above the cell surface. Activation of the integrin requires the extended open state, which binds the ligand with higher affinity than the bent closed and extended closed states. The three different classes of integrin antagonists that have been discovered so far stabilise a specific integrin conformation with most antagonists stabilising the extended high affinity integrin conformation[23,30,36]

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TGFβ and drugs targeting αvβ1 integrin could prove useful for the treatment of fibrosis.[11,45]

In addition to the above showing the important role of αv integrins in the activation of TGFβ, intrinsically linking it to fibrosis, further compelling evidence comes from studies in mice which demonstrated that the targeted conditional deletion of αv integrins from HSCs significantly inhibited fibrosis in the liver and similarly in models of lung and kidney fibrosis.[27] Hence, αv integrins are also central in the development of fibrosis[35]

2.3 | TGFβ as a target to treat fibrosis

As TGFβ plays a central role in the pathogenesis of liver fibrosis, targeting TGFβ signalling may present a therapeutic strategy for liver diseases.[46] A variety of strategies to block TGFβ signalling by targeting TGFβ isoforms or by interfering with TGFβ receptor activation have been evaluated over the years.[47] For example, the TGF-β type I receptor, also known as activin receptor-like kinase (ALK) 5 inhibitor inhibits TGFβ signalling which has been shown to prevent fibrosis in animal models of liver, lung and kidney.[48–50]

Although TGFβ could be used as a target for antifibrotic therapies, there are many concerns. This is due to TGFβ having multiple essential roles in cell differentiation, regulating cell proliferation, immune regulation, cancer surveillance and wound healing. This explains that while there have been many ALK5 small molecule inhibitors developed, few have progressed to clinical investigation due to severe cardiac toxicities in animals.[51,52] Moreover, studies in patients have not been promising, in the CAT-192 placebo-controlled clinical trial, people treated with anti-TGFβ1 monoclonal antibody reported more adverse effects than those on placebo. This re-emphasises the wide ranging critical functions of TGFβ[53] and systemic manipulation of levels is likely to incur unwanted toxic effects.[54] This has spurred the idea of targeting specific steps in TGFβ activation in a more localised manner to reduce widespread toxicity.[55]

This can be achieved through targeting integrins such as αv integrins which have a key role in the activation of latent TGFβ. The targeting of tissue or cell specific over expression of integrins could potentially permit a more precise regulation of TGFβ, rather than targeting global TGFβ activity. This potential for αv integrins being an effective antifibrotic therapy is revealed by their upregulated expression in mouse models of fibrosis and by the promising integrin inhibitor and knockout studies.[8,27]

3 | INTEGRINS AS A TARGET TO TREAT LIVER FIBROSIS

3.1 | αv integrins

The αv integrin subunit can form heterodimers with β1, β3, β5, β6 or β8 subunits[8] and activated HSCs with a myofibroblastic phenotype have been shown to express all of the known αv-containing integrins except αvβ6 integrin.[8] Most αv integrin drug discovery programmes over the past three decades have primarily focused on cancer, with some attention to fibrotic diseases.[56] Pan-αv integrin antibodies, abituzumab (EMD 525797) and intetumumab (CNTO-95) both bind to the αv subunit and prevent their cognate ligands from binding, thereby inhibiting activity. Abituzumab has been in phase 2 clinical trials for colorectal cancer and has been investigated in prostate cancer and systemic-sclerosis-associated interstitial lung disease.[57,58] Unfortunately, the clinical trial for scleroderma patients was terminated early due to difficulties in identifying participants who met the eligibility criteria.[59] Intetumumab showed early promise in the treatment of melanoma patients and was in phase 2 of clinical trials[57] but there has not been any progress since 2013 (NCT00246012).

It is important to note that αv integrins are widely expressed with wide ranging multimodal functions, hence, molecules targeting αv integrins can affect all 5 αv combinations and be prone to off-target effects.[7,60,61] For example, cilengitide, (EMD121974), an αv integrin antagonist which exerts antiangiogenic and antitumour effects preclinically, inhibits αvβ3 and αvβ5 integrins[62] but failed to improve clinical outcome in phase 3 late-stage glioblastoma trials.[58]

Another small molecule, GLPG0187, a pan αv inhibitor entered the clinic for cancer treatment. However, like cilengitide, it did not show notable clinical efficacy. Although this inhibitor targets multiple integrins, it has been shown to have acceptable safety profiles. There is a possibility that inhibition of multiple different integrins may protect against adverse effects in a similar way to that observed in pre-clinical experiments, which have shown an increased risk of vascular leak through αvβ3 integrin inhibition but protection from this may be provided through inhibition of αvβ5 integrin. From an efficacy perspective, it is not known whether inhibiting more than one αv integrin in any particular disease will deliver a better therapeutic agent clinically. Overall, application of integrin antagonists in oncology has been disappointing. One reason is the lack of preclinical evidence in the modulation of a particular biological mechanism being predictive of the clinical effect. This underpinning target validation is currently inadequate for αv integrins.[56]

As described previously, deletion of αv integrins in mouse models of liver, lung and kidney fibrosis protects mice from fibrosis. A novel inhibitor, CWHM12, a synthetic small molecule RGD peptidomimetic antagonist that targets all αv integrins, effectively treated fibrosis in both liver and lung mouse models.[27] Furthermore, CWHM12 significantly ($P < .05$) reduced cardiac fibrosis in mouse models and a similar result was observed in skeletal muscle mouse models of fibrosis.[63] In addition, MK-0429, another pan αv inhibitor, significantly ($P < .0001$) reduced kidney fibrosis in rat models.[64] Murine HSCs have been shown to express αvβ1, αvβ3, αvβ5 and αvβ8 integrins which were significantly upregulated during activation ex vivo.

In order to identify the principle αv heterodimer responsible for the antifibrotic effect, fibrosis was evaluated in mice individually depleted of the β3, β5, β6 or β8 subunits. In models of liver fibrosis in mice globally lacking αvβ3, αvβ5 and αvβ6 integrins, or conditionally deleted αvβ8 integrin, due to embryonic lethality, protection was not

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observed. This suggests that either multiple αv integrins contribute to liver fibrosis with a high degree of redundancy or that the principal integrin is αvβ1 integrin. Unfortunately, it has not been possible to evaluate the role of αvβ1 integrin in liver fibrosis in vivo as global loss is lethal in mice.[27]

3.2 | The potential role of other integrins in fibrosis

Increasing research has shown that other integrins have a similar role to αv integrins in tissue repair as matrix protein receptors. Hence, it is important to note that other integrin families beside αv integrins may also have a role in liver fibrosis and potential to be used as treatment targets.[26,65] Of the RGD-recognising integrins, αIIbβ3, α5β1 and α8β1 integrins do not contain αv integrin. Notably, α8β1 integrin shows the most promise. An anti-α8 integrin neutralising antibody was evaluated in three different mouse models of liver fibrosis and in all models, the pathology improved after administration with the α8 integrin neutralising antibody.[65,66] These findings were also shown in mouse models of pulmonary fibrosis.[67] Furthermore, α8 integrin expression was also upregulated in 90 liver fibrosis patients compared to the non-fibrotic patient controls.[66] α8 integrin was shown to be essential for the function and expression of lysyl oxidase 1, an enzyme that crosslinks and stabilises the ECM and was found to be upregulated in fibrotic liver tissue in humans as well as mice.[68] In addition, α11 integrin has also been identified as a potential therapeutic target, knockdown studies of α11 integrin in HSCs in mice models of liver fibrosis inhibited differentiation and functionality of HSCs in response to TGFβ.[69]

Nevertheless, the αv family of integrins has to date been the main research focus as there have been more studies showing the successful treatment of fibrosis using pan αv inhibitors CWHM12 or MK-0429 in various preclinical disease models, and specific αv integrins inhibitors are currently being tested in clinical trials. This indicates their potential as targets for antifibrotic therapies.[8,2770–72]

3.3 | Targeting specific αv heterodimers

One important question is whether the antifibrotic effects of pan αv inhibition are dependent upon the inhibition of multiple αv containing integrins which are found on myofibroblasts in the liver, or is there a single, dominant αv integrin mediating the antifibrotic effect observed in the preclinical models using the CWHM12 pan-αv inhibitor.[72] In general, the therapeutic targeting of specific αv integrins has shown potential as a possible treatment for patients with a broad range of fibrotic diseases.[35] Evidence from rodent models of fibrosis combined with knockout studies or pharmacologic blockade of specific integrins[27,43,45] suggests that the particular αv integrins (Table 1) or a potential combination of αv integrins involved in fibrosis is organ specific.[56] Consequently, the inhibition of specific αv integrin subunits should allow a more refined, targeted approach to TGFβ pathway inhibition to provide the desired antifibrotic effects, but with fewer undesirable side effects.[35]

Table 1 lists the inhibitors that have been developed against the specific αv heterodimers and have been assessed in active clinical trials (ie have not been withdrawn or terminated), with the exception of the inhibitor IDL-2965 where the phase 1 study was recently terminated due to the SARS-CoV-2 pandemic (NCT03949530). It also summarises the animal research related to specific αv integrins as a therapeutic target for the treatment of fibrosis.

To date, the most widely studied integrin for fibrosis is αvβ6, with αvβ6 integrin inhibitors progressing to phase 2 of clinical trials.[56] However, BG00011, an αvβ6 integrin blocking antibody, also known as STX-100, in phase 2 of clinical trials for IPF (NCT03573505), was terminated due to safety concerns. There are end-of-study and follow-up visits currently underway. Function-blocking αvβ6 integrin monoclonal antibodies have shown promise in preclinical mouse model of renal fibrosis[73] and BG00011 has also previously been used in phase 2 trials for interstitial fibrosis in kidney transplant patients (NCT00878761), but similarly was withdrawn with unspecified safety concerns. GSK3008348 is another αvβ6 integrin inhibitor which was the first inhaled small molecule αvβ6 integrin inhibitor for the treatment of IPF. Preclinical studies of this inhibitor have shown reduced TGFβ signalling and fibrotic endpoints in a mouse model of lung fibrosis, in addition to binding to the αvβ6 integrin with high affinity and selectivity in human fibrotic lung tissue, isolated lung epithelial cells and reduced TGFβ signalling in human IPF tissue slices ex vivo.[74] It was well tolerated in phase 1 clinical trials (NCT02612051) using healthy participants. Although this study was completed with the data reported,[75] there have not been any updates in further trials.

In contrast, inhibitors for liver fibrosis have not progressed as far in clinical trials. Although there have been numerous integrin inhibitors used to attenuate liver fibrosis in preclinical models (see Table 1), this has not, as yet, translated into human studies. This is likely due to the suboptimal preclinical models[76] and less attention on the liver compared to the lung and kidney. However, recently Pliant Therapeutics, Inc in collaboration with Novartis have developed a small molecule inhibitor of αvβ1 integrin, PLN-1474 for the treatment of end-stage liver fibrosis in NASH and there is currently a phase 1 trial underway.[77] Currently, there are no approved clinical therapies for fibrosis or other diseases using αv integrin inhibitors.[65] The current advantage for αv integrin inhibitors in clinical trials is their good tolerability, shown through phase 1 and 2 trials with GSK3008348[75] and PLN-74809.[78] However, many αv integrin inhibitors are not specific enough due to the pharmacophore of the inhibitors for the 5 integrins being based on the same RGD structure[65,77] and a common problem is the termination of trials due to safety concerns as demonstrated through BG00011.

The role of αvβ1 integrin in fibrosis has been difficult to study due to the promiscuity of the β1 integrin in forming heterodimers with 11 other α subunits.[72] Investigations of the role of this integrin are therefore challenging, requiring non-standard transgenic mouse approaches and the development of new experimental tools. For example, specific function-blocking antibodies against αvβ1 integrin with which to effectively and selectively study αvβ1 integrin are

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TABLE 1 Specific αv integrins and their potential involvement in fibrotic diseases through both animal and human studies with their respective inhibitors used in various animal models/clinical trials. These inhibitors developed for clinical trials have the potential to be used for other types of tissue fibrosis written in *italics* which were stated via press releases from the respective pharmaceutical company and further information on the inhibitors were provided from ClinicalTrials.gov. Unfortunately, the NCT03949530 study using IDL-2965 was terminated early due to development challenges associated with the SARS-CoV-2 pandemic and emerging non-clinical data. It is important to note that the compounds that target αvβ3 integrin also target αvβ5.[84] The cell-based potency of IDL-2965 was 1.5, 1.4 and 0.4 nM against αvβ1, αvβ3 and αvβ6 integrins, respectively, with no data available for αvβ5 integrin.[121] The inclusion criteria for the inhibitors in the preclinical studies was whether they could successfully attenuate fibrosis. N/A means that there is not an inhibitor exclusively for that integrin undergoing clinical trial. In the case of αvβ8 integrin, it has not passed the preclinical stage[58] with few studies using αvβ8 integrin and it has undergone less target validation for fibrosis which is partly due to the lack of suitably selective inhibitors[56]

Integrin	Target organ where role in fibrosis is suggested	Inhibitors undergoing clinical trials [fibrotic disease, clinical phase, trial number] and potential to work on other types tissue fibrosis	Inhibitors used in preclinical studies that lead to attenuated fibrosis [animal model]	Associated efficacy data
αvβ1	Liver, renal & pulmonary fibrosis[11,45]	N/A	Small-molecule **compound 8** (c8) [*bleomycin/CCL_4/UUO-induced pulmonary/liver/renal fibrosis in mice models*][11,45]	Ligand binding assay IC_{50} 0.089 nM IC_{50} against TGFβ activation using fibroblasts from the IPF patient lungs and murine HSCs ranged from 0.35 nM to 0.50 nM with IC_{50} of 1nM using renal fibroblasts[11,45]
αvβ3	Cardiac & lung fibrosis[89,122]	N/A	Small molecule **cilengitide** (EMD121974) [*cutaneous and pulmonary fibrosis induced by hypochlorous acid in mice models*][84,123]	Ligand binding assay IC_{50} 3nM[84]
αvβ5	Cardiac fibrosis & localized scleroderma[89,124]	None	Small molecule **cilengitide** (EMD121974) [*cutaneous and pulmonary fibrosis induced by hypochlorous acid in mice models*][84,123]	Ligand binding assay IC_{50} 37 nM[84]
αvβ6	Renal, pulmonary & biliary fibrosis[43,71,125]	N/A	Non-peptide antagonist **EMD527040** [*secondary biliary fibrosis using BDL in rat models*][115]	Ligand binding assay IC_{50} 6nM[115]
			Antibody 3G9 [*biliary fibrosis using mouse models of biliary injury/BDL, lung fibrosis using bleomycin/TGFα-induced mouse models, renal fibrosis using mouse model of Alport syndrome*][71,73,87,88,126]	IC_{50} against TGF-β activation of 3.5 pM using human β6-transfected SW480 cells[127]
αvβ8	Small airway fibrosis, biliary atresia & renal fibrosis[128–130]	None	None	
αvβ1, αvβ3 & αvβ6	N/A	**IDL-2965** [*IPF, phase 1, NCT03949530*][121] *Liver +kidney*	None	
αvβ1, & αvβ6	N/A	**PLN-74809** [*IPF, phase 2, NCT04072315 & primary sclerosing cholangitis and suspected liver fibrosis, phase 2, NCT04480840*][78,117]	None	Ligand binding assay IC_{50} <10 nM for both murine and human αvβ6 and αvβ1 IC_{50} against TGF-β activation of <200 nM[78]

BDL, bile duct ligation; CCL_4, carbon tetrachloride; IC_{50}, inhibitory concentration; IPF, idiopathic pulmonary fibrosis; TGFα, transforming growth factor α; UUO, unilateral ureteral obstruction.

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not yet available despite great efforts to generate this heterodimer-specific antibody.[56,79]

Despite this, a highly potent and specific inhibitor of the αvβ1 integrin, known as c8 has been developed. A concentration-dependent cell adhesion assay of c8 against αvβ3, αvβ5, αvβ6 and αvβ8 integrins showed IC_{50}'s of >100 000 nM with αvβ1 integrin having an IC_{50} of 0.089 ± 0.02 nM which demonstrates the selectivity of c8 for inhibiting αvβ1 integrin-mediated cell adhesion. Reports of the anti-fibrotic effects of c8 provide evidence that αvβ1 is the predominant integrin on pathologic fibroblasts responsible for activating latent TGFβ and driving tissue fibrosis in the liver and lungs. For example, administration of c8 to mice with liver or lung fibrosis, resulted in a significant down regulation of phosphorylated Smad3 protein, a downstream mediator of TGFβ signalling as observed through fluorescence intensity mapping.[11] Additional evidence for the role of β1 integrin is supported through recent studies identifying αvβ1 integrin as the major αv integrin expressed in activated primary human HSCs. C8 completely abolished TGFβ induced procollagen-1 production. Interestingly, the observed inhibition of αvβ1 integrin through these inhibitors suggest that αvβ1 integrin-mediated regulation of TGFβ-activated procollagen-1 production in HSCs is Smad3 independent. The study further suggests that αvβ1 integrin regulated procollagen-1 production is through the activation of phosphorylated extracellular-signal-regulated kinase 1/2 (ERK) also known as MAPK, a non-canonical TGF-β signalling pathway as using those inhibitors significantly inhibited TGFβ induced ERK1/2 phosphorylation levels after TGFβ treatment.[80]

Furthermore, using fetal lung fibroblasts which showed adhesion to the latency associated peptide of TGFβ was blocked by antibodies to either β1 or αv integrins, but not by antibodies to either αvβ3, αvβ5, αvβ6, or αvβ8 integrins.[11] However, additional studies using c8 have suggested that the selectivity of this compound within the β1 integrin family is poor, with high affinity also observed for α4β1 integrin. A saturation experiment with c8 and α4β1 integrin produced a dissociation constant (K_D) of 0.78 nM, comparable to αvβ1 integrin which was 0.21 nM. These studies also report that c8 had a moderate affinity for α2β1, α3β1 and α8β1 integrins which have a K_D of 11.2 nM, 13.5 nM and 8.13 nM respectively,[81] an especially pertinent finding given the emerging role of α8β1 in liver fibrosis.[66] This raises the question of whether the observed antifibrotic effects of c8 can be attributed to the inhibition of a single integrin target.

Cilengitide is a specific inhibitor of αvβ3 and αvβ5 integrins. This small molecule was suggested to be beneficial in hepatic fibrosis due to its antiproliferative and antifibrotic activity in HSCs in vitro. Compounds that target αvβ3 integrin also usually show activity at αvβ5 integrin,[82] with most existing small molecule αvβ5 integrin inhibitors displaying near-equipotency with the highly homologous αvβ3 integrin.[83] This makes it difficult to produce a selective αvβ3 and αvβ5 integrin inhibitor. Surprisingly, administering cilengitide in rat models with secondary biliary fibrosis and panlobular fibrosis due to thioacetamide worsened liver fibrosis.[84] This is in contrast to data showing β3 integrin being expressed at very low levels in quiescent rat HSCs,[85] increased αvβ3 integrin expression in both rat and human HSCs after activation in vitro, as well as αvβ3 integrin being required to sustain HSC proliferation and survival in culture. Moreover, hepatic expression of αvβ3 integrin is upregulated in bile duct ligation (BDL) and thioacetamide fibrotic livers in mice.[70] One explanation is that either cilengitide could have caused a mild increase in macrophage activation which resulted in the release of inflammatory mediators or hepatic hypoxia which could have contributed to the progression to fibrosis.[84] This highlights the need for greater understanding of the role and pattern of integrin expression both in healthy tissue and longitudinally as diseases progress, rather than only targeting integrins that are predominant in the disease state, as well as emphasising the use of human tissue samples instead of artificially induced rodent models of fibrosis.

All αv integrins apart from αvβ6 integrin are present on HSCs.[29] Studies have shown that mouse HSCs express αv, β1, β3, β5 and β8 integrins which implies expression of these specific dimers.[27] Reports from recent studies using human HSCs show similar results and highlighted that β1 and β3 integrins represent the two most abundant integrins with β5, β6 and β8 integrins showing lower abundancy in activated human HSCs via TGFβ.[80] It has been shown that β6 integrin knockout mice are protected from renal and pulmonary fibrosis.[73,86] In particular, αvβ6 integrin has been shown to be a promising target in lung fibrosis as the administration of low doses of blocking αvβ6 integrin antibodies attenuated bleomycin-induced lung fibrosis in mouse models[87] and increased levels of αvβ6 integrin were observed in patients with IPF, compared with control lung tissue.[9] This is a potential advantage as targeting αvβ6 integrin which is upregulated in diseased tissue and low in healthy could have reduced side effects compared to a target that is essential in normal tissue. There is also the additional benefit through treating the affected tissue directly and in relative isolation using inhaled drugs, such as the αvβ6 integrin inhibitor GSK3008348, which limits the potential of off-target systemic effects.[74,75] In contrast to this, in liver fibrosis, the role of αvβ6 integrin is not clear. Rodent models show αvβ6 integrin expression increases over time with liver fibrosis progression[71] but this data is not available for human liver fibrosis. This needs to be collected to inform integrin-centred strategies for pharmacological therapy of human liver disease.

3.4 | Considerations for future integrin inhibitors

Fibrosis progression requires numerous signalling pathways that interact with each other[17] and the effective abrogation of fibrosis might also require targeting these multiple pathways in concert.[35] For example, even following genetic ablation of the β6 integrin in mice there was a significant degree of lung fibrosis that developed.[88] This could be due to compensation from increased expression of other integrins, as is the case for αvβ3 and αvβ5 integrins which have been shown to compensate for each other's functions in activating TGFβ in cardiac fibroblasts.[89] This suggests that drugs targeting multiple integrins should be considered or a single compound with varying efficacy for different integrins

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should be used as they could be more successful in treating fibrosis. Furthermore, there are precedents that promiscuous drugs may offer some advantages as multiple factors contribute to the pathogenesis of a particular disease and that does not necessarily make it more toxic or cause pathways to be completely shut down or excessively activated.[90] For example, PLN-74809, a dual αvβ6/αvβ1 integrin inhibitor may have some benefit and has demonstrated good tolerability, currently being in phase 2 clinical trials as shown in Table 1.[78]

In general, there is little data on specific αv integrin expression in human liver disease. As the primary source of ECM in the liver, activated HSCs have been widely considered the most promising cellular target in liver fibrosis and their activation is a process commonly induced by various hepatic injuries.[91] HSCs and integrin expression in fibrosis are not fully elucidated and the molecular mechanisms underlying fibrosis are important for developing therapies for treatment of liver fibrosis. Additionally, as integrins are not exclusively expressed on HSCs, expression profiles for all liver cells should also be established and their contribution to liver fibrosis for each integrin in each cell type should be explored.[28] Progress has been made through recent studies showing α8β1 and α11β1 integrins exhibiting pathology-specific expression through their selective mRNA expression on activated rat HSCs in culture. Unfortunately, this was not demonstrated for αv integrins.[65] Hence, more studies exploiting the expression of specific integrin subunits and their cellular localisation within pathological tissues and other healthy organs are crucial to determine novel integrin-based therapeutic targets. The design of dimer specific drugs for specific diseases will decrease the risk of off-target effects.[7,60]

It is important to develop drugs that have selectivity between the different αv integrins as there are potential liabilities associated with the engagement of certain integrins. For example, αvβ3 and β5 integrins are involved in angiogenesis/vascular permeability and αvβ8 integrin in autoimmunity.[92] In terms of the adverse side effects of targeting specific integrin heterodimers for the treatment of liver fibrosis, the information is limited to the side effects reported from the clinical trials using BG00011 and the BDL and thioacetamide rat models of liver fibrosis using cilengitide.[84] Unfortunately, obtaining acceptable selectivity for any particular integrin can be difficult due to similarities in some of the binding sites.[93] Furthermore, sufficient potency is required to drive an antifibrotic response at a realistic clinical dose, but a compromise may be required between the ideal potency and ideal selectivity.[94] Complete blockage of a specific integrin may not be necessary as studies have suggested that low-dose partial inhibition of αvβ6 integrin-mediated TGFβ activation is sufficient to attenuate fibrosis in bleomycin-induced fibrosis in mice.[87] In addition to this, studies have been performed to assess the structure–activity relationships of a series of novel analogues of αv integrin antagonists. The activity of aryl substitutes in these analogues was compared against different αv integrins. They found that by simple variation of the position of the aryl ring, the cell adhesion potency against αvβ6 integrin can be increased and potency against αvβ3 and αvβ5 integrins reduced.[94] Further studies using a variety of aryl substituents have been performed to improve this αvβ6 integrin potency and selectivity with the aim of treating IPF in which key structure–activity relationships were identified.[95] Similar studies may be required for developing specific integrin compounds to treat liver fibrosis.

Another consideration is RGD-mimetic inhibitors or non-RGD-mimetic inhibitors. Earlier studies have shown a synthetic RGD analogue, SF-6,5, was effective in alleviating hepatic fibrosis induced by thioacetamide in rats.[96] RGD-mimetics are designed to make the same interactions as the native ligand and they include cilengitide and CWHM12.[2997] They have shown good potency but have the potential to activate integrins.[81,97] Many RGD-binding integrin inhibitors are RGD mimetics with physicochemical properties that are not compatible with oral bioavailability and compromises may have to be made between the pharmacological profile and sufficient bioavailability for clinical use.[77] There is little research showing the intracellular signalling effects of RGD-mimetics when it engages the RGD site. An approach to avoid the unwanted activation is through non-RGD-mimetic inhibitors. For instance, the non-RGD-mimetic inhibitor of αIIbβ3 integrin did not activate the integrin upon binding and will consequently prevent any unwanted signalling. However, the development of efficacious and safe drugs for this new generation of inhibitors is yet to be achieved.[77,97]

3.5 | Current treatments

Current therapeutic options for liver fibrosis are limited,[27] especially in comparison to other organs. In IPF, treatments such as pirfenidone in which the mechanism of action is not fully understood and nintedanib, an inhibitor of multiple receptor-associated tyrosine kinases have received Food and Drug Administration approval.[98] Unfortunately, most patients continue to experience disease progression and/or exacerbation despite treatment. This emphasises, that although pirfenidone and nintedanib have been approved as antifibrotic drugs, current treatments are insufficient and there is a need to develop alternative compounds.[99] Both these drugs have been used in rodent and/or patient studies to reduce fibrosis in the liver and kidney[100–102] and pirfenidone is currently undergoing a phase 2 clinical trial for advanced liver fibrosis (ClinicalTrials.gov identifier NCT04099407). However, both these drugs have not progressed beyond clinical trials which could be due to the limited understanding of their mechanisms of action and differences in fibrotic processes between organs such as the lung and liver.

There have been numerous other promising agents for the treatment of IPF, but these were terminated once they reached phase 3 clinical trials due to lack of efficacy[103] or adverse events.[104] Similar problems are observed in kidney fibrosis in which antifibrotic treatment targets such as epidermal growth factor receptor identified in preclinical studies were not successfully translated into clinical use.[105] In the case of liver fibrosis, antifibrotic agents have had even less success than for IPF.[28] Instead transplantation is often the only effective treatment for end-stage of cirrhosis. However,

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TABLE 2 Overview of phase 2 and 3 clinical trials for the treatment of liver fibrosis. These trials do not directly treat fibrosis but are mostly anti-inflammatory and/or target lipid metabolism/steatosis. Drugs listed on clinicaltrials.gov are described along with their mechanism of action and their targets.[107,111,131–136] The drugs included have a primary or secondary outcome measure as improvement in liver fibrosis and are treatments for either NAFLD, NASH, which is a subgroup of NAFLD,[76] liver fibrosis, cirrhosis or a combination of these diseases. It includes studies that are active with the exception of the Tropifexor & Cenicriviroc study (NCT03517540) in which results are still being reviewed, studies that are at phase 2 and 3 and omit drugs at phase 4, as well as ones that have been previously used for or to treat other diseases such as Type 2 Diabetes Mellitis

Drug trade name (manufacturer)	Mechanism of action	Target	Modality of the drug	Phase	Condition/ Disease	Trial identifier
Resmetirom (Madrigal Pharmaceuticals)	Agonist	THR-β	Small molecule	3	NASH	NCT03900429
Obeticholic Acid (Intercept Pharmaceuticals)	Agonist	FXR	Small molecule	3	NASH with fibrosis, NASH & compensated cirrhosis	NCT03439254 NCT02548351
Tropifexor & Cenicriviroc (Novartis Pharmaceuticals)	Agonist & Antagonist	FXR & CCR2/5	Small molecule	2b	NASH	NCT03517540
EDP-305 (Enanta Pharmaceuticals)	Agonist	FXR	Small molecule	2b	NASH	NCT04378010
Aldafermin (NGM Biopharmaceuticals, Inc)	Analogue	FGF19	Peptide	2b	NASH & compensated cirrhosis	NCT04210245
Namodenoson (Can-Fite BioPharma)	Agonist	A3 adenosine receptor	Small molecule	2b	NASH	NCT04697810
Efruxifermin (Akero Therapeutics, Inc)	Analogue	FGF21	Peptide	2b	NASH	NCT04767529
Pegbelfermin (Bristol-Myers Squibb)	Analogue	FGF21	Peptide	2 & 2b	NAFLD, NASH & liver fibrosis, NAFLD, NASH, liver fibrosis & cirrhosis, NASH	NCT04267393 NCT03486899 NCT03486912
BIO89-100 (89bio, Inc)	Analogue	FGF21	Peptide	2	NASH	NCT04048135
PF-06865571 & PF-05221304 (Pfizer)	Inhibitor	ACC & DGAT2	Small molecule	2	NAFLD & NASH with liver fibrosis	NCT04321031
BFKB8488A (Genentech, Inc)	Agonist	FGFR1/KLB receptor	Antibody	2	NASH	NCT04171765
LPCN 1144 (Lipocine)	N/A	N/A	N/A	2	NASH	NCT04134091 NCT04685993
JKB-122 (TaiwanJ Pharmaceuticals Co., Ltd)	Antagonist	TLR4	N/A	2	NASH with fibrosis	NCT04255069

ACC, acetyl-CoA carboxylase; CCR, chemokine receptor type; DGAT2, diacylglycerol O-acyltransferase 2; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FXR, farnesoid X receptor; KLB, β-klotho; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TLR4, Toll-like receptor 4; THR-β, thyroid hormone receptor β.

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with the limited donor organ availability, high cost and morbidity of transplantation,[27] there is an urgent need for effective antifibrotic therapies.[106]

Apart from therapies that address the underlying cause of liver fibrosis such as antivirals, the most promising approaches are those that focus on cellular and molecular targets that are involved in the progression or reversal of fibrosis. A prime example is developing molecules that target integrins with a disease-specific expression in myofibroblasts, one of the main drivers of disease progression.[7]

3.6 | Drug pipeline

Many antifibrotic agents are currently under investigation for liver fibrosis,[107] with 377 interventional studies listed on the clinical trials website compared with 236 for IPF. Although this demonstrates the concerted biotech/pharmaceutical effort for developing antifibrotic therapies, none have so far been licensed for the treatment of liver fibrosis. The development of novel drugs that are well tolerated and have minimal systemic side effects has been challenging. This is not a problem exclusive to liver fibrosis.[107] Furthermore, this challenge is exacerbated by the fact that existing biomarkers for liver fibrosis in clinical practice lack specificity and sensitivity[108] which makes it difficult to determine drug efficacy. Currently, liver biopsies are the gold standard for fibrosis assessment, however, due to their invasive nature and relative risk, biopsies deter patients from enrolling in trials and are an added cost for study sponsors.[107]

In an effort to overcome these difficulties, innovative methods are being developed to detect and measure fibrotic disease. This includes using high-affinity ligands and positron emission tomography (PET) to distinguish between diseased and healthy tissues. Accumulation of PET tracers in tissues provides a way to image the molecular signature of disease.[6] Furthermore, information from target engagement in vivo using PET tracers can help increase the success of drugs translated into clinical trials.[109] Studies have demonstrated that cysteine knot PET tracers have the ability to detect fibrotic lung disease in IPF patients and were associated with elevated levels of αvβ6 integrin. This showed the potential of αvβ6 integrin as a therapeutic target for IPF,[6] but has yet to be demonstrated for liver fibrosis.

Research on the mechanisms underlying fibrosis has revealed several major signalling pathways, as well as potential targets for different treatment strategies highlighted in Table 2. Strategies that target the activation of the HSCs, the major producers of excessive ECM in liver fibrosis, are also being explored.[110] For instance, obeticholic acid is a ligand for Farnesoid X receptor (FXR) receptors which is known to inhibit HSC activation and as such is being tested in clinical trials for NASH and fibrosis.[107,110]

There are currently several agents in the drug pipeline for NASH with a few in phase 3 (Table 2). However, none of these drugs target the fibrosis pathway directly and integrin targeting compounds are clearly absent from the list despite their pivotal role as important mediators of progressive fibrosis and integrin antagonism being proposed as an attractive concept to counteract liver fibrosis.[31] Many of the drugs in development act on the inflammatory processes or metabolic pathways rather than fibrosis directly.[110,111] Additionally, although there have been a few antifibrotic drugs reaching phase 3 studies, compounds have failed to progress beyond this stage. Selonsertib, an inhibitor of apoptosis signal-regulating kinase 1 (ASK1), demonstrated potent activity against its target, but in phase 3 studies it was not associated with regression of fibrosis and failed to perform better than the placebo. One possible reason for the failure of ASK1 inhibition when used alone could be due to the contribution of other pathways that mediate fibrosis in NASH.[112] Combinations of treatments that target multiple interconnected pathways present in NASH may effectively slow or reverse disease progression. Presently, there are several ongoing phase 2 combination studies and the results from these trials will play a significant role in the development of treatments for NASH.[111,113] Overall, this reveals the paucity of drugs in development that directly target fibrosis[110,111,114] and is an area that integrin targeted therapies have the potential to address.[31]

4 | CONCLUDING REMARKS

As the worldwide prevalence of CLDs is already high and increasing, there is an urgent need for effective treatment to prevent cirrhosis-related mortality[2] and targeting integrins could provide this solution.[31] For αv integrins, selectivity has been demonstrated preclinically for peptides at αvβ1 and αvβ6 integrins.[11,56] Furthermore, rodent models of liver fibrosis have shown αvβ1 and αvβ6 integrin inhibitors successfully attenuating fibrosis.[11,115]

Preclinical models have shown integrins to be a promising target in various fibrotic diseases, unfortunately, in clinical trials the same results have not been seen which emphasises the need for more data from human disease samples. There is progress being made through investment via pharmaceutical companies, such as Indalo, Pliant and Morphic.[77,116] Indalo currently has a small molecule that inhibits αvβ1, β3 and β6 integrins in clinical trials and Pliant has PLN-74809, a dual selective inhibitor of αvβ1 and αvβ6 integrins in clinical trials for IPF and liver fibrosis (Table 1). Additionally, the use of a dual integrin inhibitor is noteworthy as a potential strategic shift, and this inhibitor was compared with pirfenidone and nintedanib in lung tissue and was found to have a higher potency.[117] This further signifies the potential of integrins as an antifibrotic treatment. Moreover, Morphic is performing investigational new drug-enabling studies with a selective αvβ6 integrin small molecule inhibitor.[116]

To date, there are not any approved treatments for liver fibrosis.[28] Expectations are set high as even in a large multicentre phase III trial demonstrating the significant, yet modest effect of obeticholic acid in reducing liver fibrosis in NASH,[118] the Food and Drug Administration declined accelerated approval for the drug due to the predicted benefits being uncertain and the drug not sufficiently outweighing the potential risks.[119120] Hence, integrins could provide

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a solution as an effective antifibrotic agent. However, integrin expression in fibrosis is not fully understood, although αv integrins are described as the front runner, emerging evidence suggests α8β1 and α11β1 integrins may also be promising targets.[65,66] Studies exploiting the expression of specific integrin subunits and its cellular localisation within pathological tissues and other healthy organs are crucial to determine more successful therapeutic targets for liver fibrosis.[7]

ACKNOWLEDGEMENTS

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the UK Department of Health or GlaxoSmithKline.

CONFLICT OF INTEREST

JAR is a former employee of GlaxoSmithKline and current employee at Galecto Biotech and may own stocks or shares in both companies. KTP is a current employee at GlaxoSmithKline. GPA has served as an advisory board member for Medicines and Healthcare Products Regulatory Agency, Department of Health and Social Care, UK, Pfizer and GlaxoSmithKline; he has been a consultant to Amryt Pharmaceuticals and Astra Zeneca. SRR, JIG and AJB have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed.

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REFERENCES

1. Bataller R, Brenner DA. Liver fibrosis. *J Clin Investig*. 2005;115(2):209-218. doi: 10.1172/JCI24282
2. Marcellin P, Kutala BK. Liver diseases: a major, neglected global public health problem requiring urgent actions and large-scale screening. *Liver Int*. 2018;38:2-6. doi: 10.1111/liv.13682
3. Brenner DA. Molecular pathogenesis of liver fibrosis. *Trans Am Clin Climatol Assoc*. 2009;120:361-368.
4. Caballería L, Pera G, Arteaga I, et al. High prevalence of liver fibrosis among European adults with unknown liver disease: a population-based study. *Clin Gastroenterol Hepatol*. 2018;16(7):1138-1145.e5. doi: 10.1016/j.cgh.2017.12.048
5. Wynn TA. Cellular and molecular mechanisms of fibrosis. *J Pathol*. 2008;214(2):199-210. doi: 10.1002/path.2277
6. Kimura RH, Wang L, Shen B, et al. Evaluation of integrin αvβ6 cystine knot PET tracers to detect cancer and idiopathic pulmonary fibrosis. *Nat Communicat*. 2019;10(1): doi: 10.1038/s41467-019-11863-w
7. Schnittert J, Bansal R, Storm G, Prakash J. Integrins in wound healing, fibrosis and tumor stroma: high potential targets for therapeutics and drug delivery. *Adv Drug Delivery Rev*. 2018;129:37-53. Elsevier B.V. doi: 10.1016/j.addr.2018.01.020
8. Henderson NC, Sheppard D. Integrin-mediated regulation of TGFβ in fibrosis. *Biochem Biophys Acta*. 2013;1832(7):891-896. doi: 10.1016/j.bbadis.2012.10.005
9. Saini G, Porte J, Weinreb PH, et al. αvβ6 integrin may be a potential prognostic biomarker in interstitial lung disease. *Eur Respir J*. 2015;46(2):486-494. doi: 10.1183/09031936.00210414
10. Popov Y, Patsenker E, Stickel F, et al. Integrin αvβ6 is a marker of the progression of biliary and portal liver fibrosis and a novel target for antifibrotic therapies. *J Hepatol*. 2008;48(3):453-464. doi: 10.1016/j.jhep.2007.11.021
11. Reed NI, Jo H, Chen C, et al. The $\alpha_v\beta_1$ integrin plays a critical in vivo role in tissue fibrosis. *Sci Transl Med*. 2015;7(288):288ra79-288ra79. doi: 10.1126/scitranslmed.aaa5094
12. Jun JI, Lau LF. Resolution of organ fibrosis. *J Clin Invest*. 2018;128(1):97-107. American Society for Clinical Investigation. doi: 10.1172/JCI93563
13. Jung YK, Yim HJ. Reversal of liver cirrhosis: current evidence and expectations. *The Korean Journal of Internal Medicine*. 2017;32(2):213-228. Korean Association of Internal Medicine. doi: 10.3904/kjim.2016.268
14. Marra F, Arrighi MC, Fazi M, et al. Extracellular signal-regulated kinase activation differentially regulates platelet-derived growth factor's actions in hepatic stellate cells, and is induced by in vivo liver injury in the rat. *Hepatology*. 1999;30(4):951-958. doi: 10.1002/hep.510300406
15. Seki E, Schwabe RF. Hepatic inflammation and fibrosis: functional links and key pathways. *Hepatology (Baltimore, MD)*. 2015;61(3):1066. doi: 10.1002/HEP.27332
16. Trautwein C, Friedman SL, Schuppan D, Pinzani M. Hepatic fibrosis: concept to treatment. *J Hepatol*. 2015;62(1):S15-S24. doi: 10.1016/J.JHEP.2015.02.039
17. Lee UE, Friedman SL. Mechanisms of hepatic fibrogenesis. *Best Pract Res Clin Gastroenterol*. 2011;25(2):195-206. doi: 10.1016/j.bpg.2011.02.005
18. Fabregat I, Moreno-Càceres J, Sánchez A, et al. TGF-β signalling and liver disease. *FEBS J*. 2016;283(12):2219-2232. doi: 10.1111/febs.13665
19. Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology*. 2008;134(6):1655-1669. doi: 10.1053/j.gastro.2008.03.003
20. Khan Z, Marshall JF. The role of integrins in TGFβ activation in the tumour stroma. *Cell Tissue Res*. 2016;365(3):657-673. Springer Verlag. doi: 10.1007/s00441-016-2474-y
21. Higashi T, Friedman SL, Hoshida Y. Hepatic stellate cells as key target in liver fibrosis. *Adv Drug Delivery Rev*. 2017;121:27-42. Elsevier B.V. doi: 10.1016/j.addr.2017.05.007
22. Hamidi H, Ivaska J. Every step of the way: integrins in cancer progression and metastasis. *Nat Rev Cancer*. 2018;18(9):1-16. doi: 10.1038/s41568-018-0038-z
23. Springer TA, Dustin ML. Integrin inside-out signaling and the immunological synapse. *Curr Opin Cell Biol*. 2012;24(1):107-115. NIH Public Access. doi: 10.1016/j.ceb.2011.10.004
24. Goodman SL, Picard M. Integrins as therapeutic targets. *Trends Pharmacol Sci*. 2012;33(7):405-412. doi: 10.1016/j.tips.2012.04.002
25. Humphries JD, Byron A, Humphries MJ. Integrin ligands at a glance. *J Cell Sci*. 2006;119(19):3901-3903. doi: 10.1242/JCS.03098
26. Margadant C, Sonnenberg A. Integrin–TGF-β crosstalk in fibrosis, cancer and wound healing. *EMBO Rep*. 2010;11(2):97-105. doi: 10.1038/embor.2009.276
27. Henderson NC, Arnold TD, Katamura Y, et al. Targeting of αv integrin identifies a core molecular pathway that regulates fibrosis in several organs. *Nat Med*. 2013;19(12):1617-1624. doi: 10.1038/nm.3282
28. Schuppan D, Ashfaq-Khan M, Yang AT, Kim YO. Liver fibrosis: direct antifibrotic agents and targeted therapies. *Matrix Biol*. 2018;68-69:435-451. doi: 10.1016/j.matbio.2018.04.006
29. Hintermann & Christen. The many roles of cell adhesion molecules in hepatic fibrosis. *Cells*. 2019;8(12):1503. doi: 10.3390/cells8121503
30. Li J, Springer TA. Integrin extension enables ultrasensitive regulation by cytoskeletal force. *Proc Natl Acad Sci USA*. 2017;114(18):4685-4690. doi: 10.1073/pnas.1704171114

14783231, 2022, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15157 by Cochrane France, Wiley Online Library on [24/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

31. Patsenker E, Stickel F. Role of integrins in fibrosing liver diseases. *Am J Physiol-Gastr Liver Physiol*. 2011;301(3):G425-G434. doi: 10.1152/ajpgi.00050.2011
32. Thomas JR, Paul NR, Morgan MR. Adhesion and growth factor receptor crosstalk mechanisms controlling cell migration. *Ess Biochem*. 2019;63(5):553-567. Portland Press Ltd. doi: 10.1042/EBC20190025
33. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet*. 2006;7(8):606-619. Nature Publishing Group. doi: 10.1038/nrg1879
34. Wei Z, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. *Cell Res* 2002;12(1):9–18. Nature Publishing Group. doi: 10.1038/sj.cr.7290105
35. Conroy KP, Kitto LJ, Henderson NC. αv integrins: key regulators of tissue fibrosis. *Cell Tissue Res*. 2016;365(3):511-519. 10.1007/s00441-016-2407-9
36. Shimaoka M, Springer TA. Therapeutic antagonists and conformational regulation of integrin function. *Nat Rev Drug Discov*. 2003;2(9):703-716. European Association for Cardio-Thoracic Surgery. doi: 10.1038/nrd1174
37. Estevez B, Shen B, Du X. Targeting integrin and integrin signaling in treating thrombosis. *Arterioscler Thromb Vasc Biol*. 2015;35(1):24. doi: 10.1161/ATVBAHA.114.303411
38. Ley K, Rivera-Nieves J, Sandborn WJ, Shattil S. Integrin-based therapeutics: biological basis, clinical use and new drugs. *Nat Rev Drug Discov*. 2016;15(3):173-183. Nature Publishing Group. doi: 10.1038/nrd.2015.10
39. Munger JS, Sheppard D. Cross talk among TGF-β signaling pathways, integrins, and the extracellular matrix. *Cold Spring Harbor Perspectives in Biology*. 2011;3(11):a005017. doi: 10.1101/cshperspect.a005017.a005017
40. Heino J, Ignotz RA, Hemler ME, Crouse C, Massague J. Regulation of cell adhesion receptors by transforming growth factor-beta. Concomitant regulation of integrins that share a common beta 1 subunit - PubMed. *J Biol Chem*. 1989;264:380-388.
41. Ignotz RA, Heino J, Massague J. Regulation of cell adhesion receptors by transforming growth factor-β. Regulation of vitronectin receptor and LFA-1. *J Biol Chem*. 1989;264(1):389-392.
42. Zambruno G, Marchisio PC, Marconi A, et al. Transforming growth factor-β1 modulates β1 and β5 integrin receptors and induces the de novo expression of the avβ6 heterodimer in normal human keratinocytes: Implications for wound healing. *J Cell Biol*. 1995;129(3):853-865. doi: 10.1083/jcb.129.3.853
43. Ma LJ, Yang H, Gaspert A, et al. Transforming growth factor-β-dependent and -independent pathways of induction of tubulointerstitial fibrosis in β6-/- mice. *Am J Pathol*. 2003;163(4):1261-1273. doi: 10.1016/S0002-9440(10)63486-4
44. Munger JS, Huang X, Kawakatsu H, et al. The integrin αvβ6 binds and activates latent TGFβ1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell*. 1999;96(3):319-328. doi: 10.1016/S0092-8674(00)80545-0
45. Chang Y, Lau WL, Jo H, et al. Pharmacologic blockade of αvβ1 integrin ameliorates renal failure and fibrosis in Vivo. *J Am Soc Nephrol*. 2017;28(7):1998-2005. doi: 10.1681/ASN.2015050585
46. Xu F, Liu C, Zhou D, Zhang L. TGF-β/SMAD pathway and its regulation in hepatic fibrosis. *J Histochem Cytochem*. 2016;64(3):157-167. Histochemical Society Inc. doi: 10.1369/0022155415627681
47. Györfi AH, Matei AE, Distler JHW. Targeting TGF-β signaling for the treatment of fibrosis. *Matr Biol*. 2018;68-69:8-27. Elsevier B.V. doi: 10.1016/j.matbio.2017.12.016
48. Bonniaud P, Margetts PJ, Kolb M, et al. Progressive transforming growth factor β1-induced lung fibrosis is blocked by an orally active ALK5 kinase inhibitor. *Am J Respir Crit Care Med*. 2005;171(8):889-898. doi: 10.1164/rccm.200405-612OC
49. De Gouville AC, Boullay V, Krysa G, et al. Inhibition of TGF-β signaling by an ALK5 inhibitor protects rats from dimethylnitrosamine-induced liver fibrosis. *Br J Pharmacol*. 2005;145(2):166-177. doi: 10.1038/sj.bjp.0706172
50. Petersen M, Thorikay M, Deckers M, et al. Oral administration of GW788388, an inhibitor of TGF-β type I and II receptor kinases, decreases renal fibrosis. *Kidney Int*. 2008;73(6):705-715. doi: 10.1038/sj.ki.5002717
51. Herbertz S, Sawyer JS, Stauber AJ, et al. Clinical development of galunisertib (LY2157299 monohydrate), a small molecule inhibitor of transforming growth factor-beta signaling pathway. *Drug Des Devel Ther*. 2015;9:4479-4499. Dove Medical Press Ltd. doi: 10.2147/DDDT.S86621
52. van Beuge MM, Prakash J, Lacombe M, et al. Enhanced effectivity of an ALK5-inhibitor after cell-specific delivery to hepatic stellate cells in mice with liver injury. *PLoS One*. 2013;8(2):e56442. doi: 10.1371/journal.pone.0056442
53. Morikawa M, Derynck R, Miyazono K. TGF-β and the TGF-β family: context-dependent roles in cell and tissue physiology. *Cold Spring Harbor Persp Biol*. 2016;8(5):a021873. doi: 10.1101/cshperspect.a021873.a021873
54. Denton CP, Merkel PA, Furst DE. Recombinant human anti–transforming growth factor β1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. *Arthritis Rheum*. 2007;56(1):323-333. doi: 10.1002/art.22289
55. Mehal W, Schuppan D. Antifibrotic therapies in the liver. *Semin Liver Diseases*. 2015;35(02):184-198. doi: 10.1055/s-0035-1550055
56. Hatley RJD, Macdonald SJF, Slack RJ, Le J, Ludbrook SB, Lukey PT. An αv-RGD integrin inhibitor toolbox: drug discovery insight, challenges and opportunities. *Angew Chem Int Ed*. 2018;57(13):3298-3321. doi: 10.1002/anie.201707948
57. O'Day S, Pavlick A, Loquai C, et al. A randomised, phase II study of intetumumab, an anti-α v-integrin mAb, alone and with dacarbazine in stage IV melanoma. *Br J Cancer*. 2011;105(3):346-352. doi: 10.1038/bjc.2011.183
58. Raab-Westphal S, Marshall JF, Goodman SL. Integrins as therapeutic targets: successes and cancers. *Cancers*. 2017;9(12):110. MDPI AG. doi: 10.3390/cancers9090110
59. Lodyga M, Hinz B. TGF-β1 – A truly transforming growth factor in fibrosis and immunity. *Semin Cell Devel Biol*. 2020;101:123-139. Elsevier Ltd. doi: 10.1016/j.semcdb.2019.12.010
60. Hynes RO. Integrins: Bidirectional, allosteric signaling machines. *Cell*. 2002;110(6):673-687. doi: 10.1016/S0092-8674(02)00971-6
61. Lowell CA, Mayadas TN. Overview: studying integrins in vivo. *Meth Mol Biol*. 2011;757:369-397. doi: 10.1007/978-1-61779-166-6_22
62. Alghisi GC, Ponsonnet L, Rüegg C. The integrin antagonist cilengitide activates αVβ3, disrupts VE-cadherin localization at cell junctions and enhances permeability in endothelial cells. *PLoS One*. 2009;4(2):e4449. doi: 10.1371/journal.pone.0004449
63. Murray IR, Gonzalez ZN, Baily J, et al. αv integrins on mesenchymal cells regulate skeletal and cardiac muscle fibrosis. *Nat Commun*. 2017;8(1):1-13. doi: 10.1038/s41467-017-01097-z
64. Zhou X, Zhang J, Haimbach R, et al. An integrin antagonist (MK-0429) decreases proteinuria and renal fibrosis in the ZSF1 rat diabetic nephropathy model. *Pharmacol Res Persp*. 2017;5(5):e00354. doi: 10.1002/prp2.354
65. Yokosaki Y, Nishimichi N. New therapeutic targets for hepatic fibrosis in the integrin family, α8β1 and α11β1, induced specifically on activated stellate cells. *Int J Mol Sci*. 2021;22(23):12794. doi: 10.3390/IJMS222312794
66. Nishimichi N, Tsujino K, Kanno K, et al. Induced hepatic stellate cell integrin, α8β1, enhances cellular contractility and TGFβ activity in liver fibrosis. *J Pathol*. 2021;253(4):366. doi: 10.1002/PATH.5618

14783231, 2022, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15157 by Cochrane France, Wiley Online Library on [24/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

67. Nishimichi N, Kanno K, Sentani K, Yasui W, Yokosaki Y. A possible therapeutic agent for pulmonary fibrosis: antibody against integrin α8β1. *Eur Respir J*. 2013;42(Suppl 57):P4885.
68. Yang A, Yan X, Xu H, et al. Selective depletion of hepatic stellate cells-specific LOXL1 alleviates liver fibrosis. *FASEB J: Off Publ the Fed Am Soc Exp Biol*. 2021;35(10):e21918. doi: 10.1096/FJ.202100374R
69. Bansal R, Nakagawa S, Yazdani S, et al. Integrin alpha 11 in the regulation of the myofibroblast phenotype: implications for fibrotic diseases. *Exp Mol Med*. 2017;49(11):e396. doi: 10.1038/EMM.2017.213
70. Li Y, Pu S, Liu Q, et al. An integrin-based nanoparticle that targets activated hepatic stellate cells and alleviates liver fibrosis. *J Controlled Release*. 2019;303:77-90. doi: 10.1016/j.jconrel.2019.04.022
71. Peng Z-W, Ikenaga N, Liu SB, et al. Integrin αvβ6 critically regulates hepatic progenitor cell function and promotes ductular reaction, fibrosis, and tumorigenesis. *Hepatology (Baltimore, MD)*. 2016;63(1):217-232. doi: 10.1002/hep.28274
72. Smith JR, Henderson NC. Recent progress on targeting the αvβ1 integrin for the treatment of tissue fibrosis. *Exp Opin Drug Discov*. 2016;11(8):749-751. Taylor and Francis Ltd. doi: 10.1080/17460441.2016.1193486
73. Hahm K, Lukashev ME, Luo Y, et al. αvβ6 integrin regulates renal fibrosis and inflammation in alport mouse. *Am J Pathol*. 2007;170(1):110-125. doi: 10.2353/ajpath.2007.060158
74. John AE, Graves RH, Pun KT, et al. Translational pharmacology of an inhaled small molecule αvβ6 integrin inhibitor for idiopathic pulmonary fibrosis. *Nat Commun*. 2020;11(1):1-14. doi: 10.1038/s41467-020-18397-6
75. Maden CH, Fairman D, Chalker M, et al. Safety, tolerability and pharmacokinetics of GSK3008348, a novel integrin αvβ6 inhibitor, in healthy participants. *Eur J Clin Pharmacol*. 2018;74(6):701-709. doi: 10.1007/s00228-018-2435-3
76. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism*. 2016;65(8):1038-1048. doi: 10.1016/j.metabol.2015.12.012
77. Slack RJ, Macdonald SJF, Roper JA, Jenkins RG, Hatley RJD. Emerging therapeutic opportunities for integrin inhibitors. *Nat Rev Drug Discovery*. 2021;2021:1-19. doi: 10.1038/s41573-021-00284-4
78. Turner S, Lepist EI, Rock F, et al. Late breaking abstract - PK/PD assessment of an oral, selective aVß6/aVß1 integrin dual antagonist, PLN-74809, for the treatment of idiopathic pulmonary fibrosis. *Eur Respir J*. 2019;54(suppl 63):PA1298. doi: 10.1183/13993003.congress-2019.pa1298
79. Song K-H, Cho S-J, Song J-Y. αvβ1 integrin as a novel therapeutic target for tissue fibrosis. *Ann Translat Med*. 2016;4(20):411. doi: 10.21037/atm.2016.10.33
80. Han Z, Ma Y, Cao G, et al. Integrin αVβ1 regulates procollagen I production through a non-canonical transforming growth factor β signaling pathway in human hepatic stellate cells. *Biochem J*. 2021;478(9):1689-1703. doi: 10.1042/BCJ20200749
81. Wilkinson AL, Barrett JW, Slack RJ. Pharmacological characterisation of a tool αvβ1 integrin small molecule RGD-mimetic inhibitor. *Eur J Pharmacol*. 2019;842:239-247. doi: 10.1016/j.ejphar.2018.10.045
82. Liu Z, Wang F, Chen X. Integrin αvβ3-targeted cancer therapy. *Drug Devel Res*. 2008;69(6):329-339. NIH Public Access. doi: 10.1002/ddr.20265
83. Lippa RA, Barrett J, Pal S, Rowedder JE, Murphy JA, Barrett TN. Discovery of the first potent and selective αvβ5 integrin inhibitor based on an amide-containing core. *Eur J Med Chem*. 2020;208:112719. doi: 10.1016/j.ejmech.2020.112719
84. Patsenker E, Popov Y, Stickel F, et al. Pharmacological inhibition of integrin αvβ3 aggravates experimental liver fibrosis and suppresses hepatic angiogenesis. *Hepatology*. 2009;50(5):1501-1511. doi: 10.1002/hep.23144
85. Zhou X, Murphy FR, Gehdu N, Zhang J, Iredale JP, Benyon RC. Engagement of αvβ3 integrin regulates proliferation and apoptosis of hepatic stellate cells. *J Biol Chem*. 2004;279(23):23996-24006. doi: 10.1074/jbc.M311668200
86. Pittet JF, Griffiths MJD, Geiser T, et al. TGF-β is a critical mediator of acute lung injury. *J Clin Invest*. 2001;107(12):1537-1544. doi: 10.1172/JCI11963
87. Horan GS, Wood S, Ona V, et al. Partial inhibition of integrin αvβ6 prevents pulmonary fibrosis without exacerbating inflammation. *Am J Respir Crit Care Med*. 2008;177(1):56-65. doi: 10.1164/rccm.200706-805OC
88. Madala SK, Korfhagen TR, Schmidt S, et al. Inhibition of the αvβ6 integrin leads to limited alteration of TGF-α-induced pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol*. 2014;306(8):L726. doi: 10.1152/ajplung.00357.2013
89. Sarrazy V, Koehler A, Chow ML, et al. Integrins αvβ5 and αvβ3 promote latent TGF-β1 activation by human cardiac fibroblast contraction. *Cardiovasc Res*. 2014;102(3):407-417. doi: 10.1093/cvr/cvu053
90. Mencher SK, Wang LG. Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). *BMC Clin Pharmacol*. 2005;5: doi: 10.1186/1472-6904-5-3
91. He L, Yuan H, Liang J, Hong J, Qu C. Expression of hepatic stellate cell activation-related genes in HBV-, HCV-, and nonalcoholic fatty liver disease-associated fibrosis. *PLoS One*. 2020;15(5):e0233702. doi: 10.1371/journal.pone.0233702
92. Rowedder JE, Ludbrook SB, Slack RJ. Determining the true selectivity profile of αv integrin ligands using radioligand binding: applying an old solution to a new problem. *SLAS DISCOVERY Adv Sci Drug Discovery*. 2017;22(8):962-973. doi: 10.1177/2472555217703908
93. Anderson NA, Campos S, Butler S, et al. Discovery of an orally bioavailable pan αv integrin inhibitor for idiopathic pulmonary fibrosis. *J Med Chem*. 2019;62(19):8796-8808. doi: 10.1021/acs.jmedchem.9b00962
94. Adams J, Anderson EC, Blackham EE, et al. Structure activity relationships of αv integrin antagonists for pulmonary fibrosis by variation in aryl substituents. *ACS Med Chem Lett*. 2014;5(11):1207-1212. doi: 10.1021/ml5002079
95. Procopiou PA, Anderson NA, Barrett J, et al. Discovery of (S)-3-(3-(3,5-Dimethyl-1 H-pyrazol-1-yl)phenyl)-4-((R)-3-(2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)ethyl)pyrrolidin-1-yl)butanoic acid, a nonpeptidic αvβ6 integrin inhibitor for the inhaled treatment of idiopathic pulmonary fibrosis. *J Med Chem*. 2018;61(18):8417-8443. doi: 10.1021/acs.jmedchem.8b00959
96. Bruck R, Hershkoviz R, Lider O, Shirin H, Aeed H, Halpern Z. The use of synthetic analogues of Arg-Gly-Asp (RGD) and soluble receptor of tumor necrosis factor to prevent acute and chronic experimental liver injury. *Yale J Biol Med*. 1997;70(4):391-402.
97. Miller LM, Pritchard JM, Macdonald SJF, Jamieson C, Watson AJB. Emergence of small-molecule non-RGD-mimetic inhibitors for RGD integrins. *J Med Chem*. 2017;60(8):3241-3251. doi: 10.1021/acs.jmedchem.6b01711
98. Trawinska MA, Rupesinghe RD, Hart SP. Patient considerations and drug selection in the treatment of idiopathic pulmonary fibrosis. *Ther Clin Risk Manag*. 2016;12:563-574. Dove Medical Press Ltd. doi: 10.2147/TCRM.S81144
99. Somogyi V, Chaudhuri N, Torrisi SE, Kahn N, Müller V, Kreuter M. The therapy of idiopathic pulmonary fibrosis: what is next? *Eur Resp Rev*. 2019;28(153):190021. doi: 10.1183/16000617.0021-2019
100. Liu F, Wang L, Qi H, et al. Nintedanib, a triple tyrosine kinase inhibitor, attenuates renal fibrosis in chronic kidney disease. *Clin Sci*. 2017;131(16):2125-2143. doi: 10.1042/CS20170134
101. Lopez-de la Mora DA, Sanchez-Roque C, Montoya-Buelna M, et al. Role and new insights of pirfenidone in fibrotic diseases. *Int J Med Sci*. 2015;12(11):840-847. doi: 10.7150/ijms.11579
102. Wollin L, Togbe D, Ryffel B. Effects of nintedanib in an animal model of liver fibrosis. *Biomed Res Int*. 2020;2020:1-9. doi: 10.1155/2020/3867198

14783231, 2022, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15157 by Cochrane France, Wiley Online Library on [24/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

103. Aryal S, Nathan SD. An update on emerging drugs for the treatment of idiopathic pulmonary fibrosis. *Exp Opin Emerg Drugs*. 2018;23(2):159-172. Taylor and Francis Ltd. doi: 10.1080/14728214.2018.1471465
104. Saito S, Alkhatib A, Kolls JK, Kondoh Y, Lasky JA. Pharmacotherapy and adjunctive treatment for idiopathic pulmonary fibrosis (IPF). *J Thor Diseases*. 2019;11(S14):S1740-S1754. AME Publishing Company. 10.21037/jtd.2019.04.62
105. Klinkhammer BM, Goldschmeding R, Floege J, Boor P. Treatment of renal fibrosis—turning challenges into opportunities. *Adv Chron Kidn Disease*. 2017;24(2):117-129. W.B. Saunders. doi: 10.1053/j.ackd.2016.11.002
106. Böttcher K, Pinzani M. Pathophysiology of liver fibrosis and the methodological barriers to the development of anti-fibrogenic agents. *Adv Drug Deliv Rev*. 2017;121:3-8. doi: 10.1016/j.addr.2017.05.016
107. Trivella JP, Martin P, Carrion AF. Novel targeted therapies for the management of liver fibrosis. *Exp Opin Emerg Drugs*. 2020;25(1):59-70. Taylor and Francis Ltd. doi: 10.1080/14728214.2020.1735350
108. Nallagangula KS, Nagaraj SK, Venkataswamy L, Chandrappa M. Liver fibrosis: a compilation on the biomarkers status and their significance during disease progression. *Future Sci OA*. 2018;4(1):FSO250 Future Medicine Ltd. doi: 10.4155/fsoa-2017-0083
109. Campbell BR, Gonzalez Trotter D, Hines CDG, et al. In Vivo imaging in pharmaceutical development and its impact on the 3Rs. *ILAR J*. 2016;57(2):212-220. doi: 10.1093/ilar/ilw019
110. Santoro R, Mangia A. Progress in promising anti-fibrotic therapies. *Exp Rev Gastroenterol Hepatol*. 2019;13(12):1145-1152. Taylor and Francis Ltd. doi: 10.1080/17474124.2019.1688659
111. Romero FA, Jones CT, Xu Y, Fenaux M, Halcomb RL. The race to bash NASH: emerging targets and drug development in a complex liver disease. *J Med Chem*. 2020;63(10):5031-5073. doi: 10.1021/acs.jmedchem.9b01701
112. Harrison SA, Wai-Sun Wong V, Okanoue T, et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: results from randomized Ph III STELLAR trials. *J Hepatol*. 2020;73:26-39. doi: 10.1016/j.jhep.2020.02.027
113. Albhaisi SAM, Sanyal AJ. New drugs for NASH. *Liver Int*. 2021;41(S1):112-118. doi: 10.1111/LIV.14844
114. Cho ME, Kopp JB. Pirfenidone: an anti-fibrotic therapy for progressive kidney disease. *Exp Opin Invest Drugs*. 2010;19(2):275-283. NIH Public Access. doi: 10.1517/13543780903501539
115. Patsenker E, Popov Y, Stickel F, Jonczyk A, Goodman SL, Schuppan D. Inhibition of Integrin αvβ6 on cholangiocytes blocks transforming growth factor-β activation and retards biliary fibrosis progression. *Gastroenterology*. 2008;135(2):660-670. doi: 10.1053/j.gastro.2008.04.009
116. Rauchman M, Griggs D. Emerging strategies to disrupt the central TGF-β axis in kidney fibrosis. *Translat Res*. 2019;209:90-104. Mosby Inc. doi: 10.1016/j.trsl.2019.04.003
117. Decaris M, Schaub J, Chen C, et al. Dual aVß6/aVß1 inhibitor PLN-74809 blocks multiple TGF-ß activation pathways associated with IPF. *Eur Respir J*. 2019;54(suppl 63):PA1286. doi: 10.1183/13993003.congress-2019.pa1286
118. Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019;394(10215):2184-2196. doi: 10.1016/S0140-6736(19)33041-7
119. Intercept Pharmaceuticals, Inc. Intercept Receives Complete Response Letter from FDA for Obeticholic Acid for the Treatment of Fibrosis Due to NASH. 2020. https://ir.interceptpharma.com/news-releases/news-release-details/intercept-receives-complete-response-letter-fda-obeticholic-acid Accessed October 5, 2020.
120. Vuppalanchi R, Noureddin M, Alkhouri N, Sanyal AJ. Therapeutic pipeline in nonalcoholic steatohepatitis. *Nat Rev Gastroenterol Hepatol*. 2021;18(6):373-392. doi: 10.1038/s41575-020-00408-y
121. Kossen K, Schaefer C, Lim S, et al. IDL-2965: a selective, highly-potent, oral integrin antagonist for IPF. *Eur Respir J*. 2019;54(suppl 63):PA5374. doi: 10.1183/13993003.congress-2019.pa5374
122. Fiore VF, Wong SS, Tran C, et al. αvβ3 Integrin drives fibroblast contraction and strain stiffening of soft provisional matrix during progressive fibrosis. *JCI. Insight*. 2018;3(20): doi: 10.1172/jci.insight.97597
123. Bagnato GL, Irrera N, Pizzino G, et al. Dual αvβ3 and avβ5 blockade attenuates fibrotic and vascular alterations in a murine model of systemic sclerosis. *Clin Sci*. 2018;132(2):231-242. doi: 10.1042/CS20171426
124. Asano Y, Ihn H, Jinnin M, Mimura Y, Tamaki K. Involvement of αvβ5 integrin in the establishment of autocrine TGF-β signaling in dermal fibroblasts derived from localized scleroderma. *J Investig Dermatol*. 2006;126(8):1761-1769. doi: 10.1038/sj.jid.5700331
125. Coward WR, Saini G, Jenkins G. The pathogenesis of idiopathic pulmonary fibrosis. *Ther Adv Respirat Disease*. 2010;4(6):367-388. doi: 10.1177/1753465810379801
126. Wang B, Dolinski BM, Kikuchi N, et al. Role of αvβ6 integrin in acute biliary fibrosis. *Hepatology*. 2007;46(5):1404-1412. doi: 10.1002/hep.21849
127. Weinreb PH, Simon KJ, Rayhorn P, et al. Function-blocking integrin αvβ6 monoclonal antibodies: distinct ligand-mimetic and nonligand-mimetic classes. *J Biol Chem*. 2004;279(17):17875-17887. doi: 10.1074/jbc.M312103200
128. Iordanskaia T, Koeck E, Rossi C, et al. Integrin β-8, but not β-5 or -6, protein expression is increased in livers of children with biliary atresia. *J Pediatr Gastroenterol Nutr*. 2014;59(6):679-683. doi: 10.1097/MPG.0000000000000518
129. McCarty JH. αvβ8 integrin adhesion and signaling pathways in development, physiology and disease. *J Cell Sci*. 2020;133(12). NLM (Medline). doi: 10.1242/jcs.239434
130. Minagawa S, Lou J, Seed RI, et al. Selective targeting of TGF-β activation to treat Fibroinflammatory airway disease. *Sci Transl Med*. 2014;6(241):241ra79. doi: 10.1126/scitranslmed.3008074
131. Esler WP, Bence KK. Metabolic targets in nonalcoholic fatty liver disease. *Cell Mol Gastroenterol Hepatol*. 2019;8(2):247–267. Elsevier Inc. 10.1016/j.jcmgh.2019.04.007
132. Finan B, Parlee SD, Yang B. Nuclear hormone and peptide hormone therapeutics for NAFLD and NASH. *Mol Metabol*. 2021;46: doi: 10.1016/J.MOLMET.2020.101153
133. Fishman P, Cohen S, Itzhak I, et al. The A3 adenosine receptor agonist, namodenoson, ameliorates non-alcoholic steatohepatitis in mice. *Int J Mol Med*. 2019;44(6):2256-2264. doi: 10.3892/IJMM.2019.4364
134. Harrison SA, Ruane PJ, Freilich BL, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2A trial. *Nat Med*. 2021;27(7):1262–1271. doi: 10.1038/s41591-021-01425-3
135. Hsu MC, Liu SH, Wang CW, et al. JKB-122 is effective, alone or in combination with prednisolone in Con A-induced hepatitis. *Eur J Pharmacol*. 2017;812:113-120. doi: 10.1016/j.ejphar.2017.07.012
136. Sonoda J, Chen MZ, Baruch A. FGF21-receptor agonists: an emerging therapeutic class for obesity-related diseases. *Horm Mol Biol Clin Inv*. 2017;30(2). Walter de Gruyter GmbH; doi: 10.1515/hmbci-2017-0002

How to cite this article: Rahman SR, Roper JA, Grove JI, Aithal GP, Pun KT, Bennett AJ. Integrins as a drug target in liver fibrosis. *Liver Int*. 2022;42:507–521. doi:10.1111/liv.15157

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